

REMARKS

1. Claims

Claims 67-69, 73-85, 87, 90-110, 112 and 113 are pending in this application, with claim 67 being independent.

Claims 67 is amended herein to more particularly point out the claimed subject matter and to delete extraneous language.

The present amendment is supported by the original disclosure and no new matter has been added. Specifically, support for the present amendment can be found in the original disclosure at page 32, paragraph 0131. The above amendment should not be construed as constituting any admission with respect to the patentability of the previously claimed subject matter, and Applicants reserve the right to pursue any canceled subject matter in one or more continuing patent applications.

2. The Rejection of Claims 67-69, 73-85, 90-110, 112 and 113 under 35 USC § 103(a) is Obviated

In the Office Action of November 16, 2005, Examiner rejected then-pending claims 67-69, 73-85, 90-110, 112 and 113 as allegedly being unpatentable over Rubin *et al.* (U.S. Pat. No. 5,925,334) in view of Schmitt *et al.* (U.S. Pat No. 4,950,477) and Saunders Manual of Medical Practice. Applicants respectfully traverse this rejection.

Examiner alleges that Rubin *et al.* teach a surfactant such as DPPC and ExoSurf[®] mixed with an aerosolizing agent to promote mucus clearance and that the use of such surfactants lowers the surface tension to enhance distribution and spreading of other medications *to the lower respiratory tract* such as, for example, a surfactant and an antibiotic or a surfactant and an inhaled anti-inflammatory agent. (Emphasis Added). In addition, the Examiner alleges that Rubin *et al.* teach methods of administration of the surfactant composition via a metered dose inhaler, dry powder inhalation, jet nebulization and ultrasonic nebulization. Further, the Examiner states that Rubin *et al.* does not teach particle size, the osmolality, pH, or the NaCl equivalency of the composition.

Thus, Examiner relies on Rubin *et al.* solely for the proposition that surfactants can lower the surface tension to enhance distribution and spreading of other medications *to the lower respiratory tract*.

Examiner cites Schmitt *et al.* as allegedly teaching a non-antimicrobial antibiotic and to provide motivation for the instantly claimed particle size. The Examiner alleges that Schmitt *et al.* teach that particle size is important because particles smaller than 0.5 μm are exhaled and thus not retained *in the lungs* while particles greater than 8.0 μm such as those produced in an atomizer *do not reach the periphery of the lungs* and are therefore not effective in preventing or treating infection. In addition, the Examiner states that Schmitt *et al.* does not teach the treatment of sinusitis and likewise fails to teach or mention osmolality and NaCL equivalency.

Thus, Examiner relies on Schmitt *et al.* solely for the proposition that a particle size of between 0.5 μm and 8.0 μm is necessary for the particles to *reach the periphery of the lungs and be retained therein* to achieve a therapeutic effect in the prevention or treatment of an infection within the lung.

Examiner cites to Saunders Manual of Medical Practice as allegedly teaching the state of the art regarding treatment of sinusitis. The Examiner alleges that Saunders Manual teaches that sinusitis is an inflammation of one or more paranasal sinuses but usually refers to infection of the sinuses. Further, the Examiner alleges that Saunders Manual teaches that there may be an overlap between symptoms of acute or chronic sinusitis and other causes of nasal congestion such as allergic or viral rhinitis. In addition, the Examiner alleges that Saunders Manual teaches that treatment includes antibiotics such as amoxicillin/clavulanate along with decongestants, mucolytics and other ciliator activators, nasal corticosteroids, antihistamines and saline. Lastly, the Examiner correctly states Saunders Manual fails to teach intra-nasal administration of the agents except the corticosteroids and likewise fails to teach particle size, osmolality and NaCl equivalency of the composition.

Thus, the Examiner relies on Saunders Manual solely for the proposition that antibiotics, decongestants, mucolytics, nasal corticosteroids and anti-histamines were known to be used in the treatment of sinusitis.

Based upon the alleged teachings of Rubin *et al.*, in view of Schmitt *et al.* and Saunders Manual discussed *supra*, the Examiner makes the conclusory statement that it would have been obvious to a person of skill in the art at the time the invention was made to combine the surfactants/antibiotics/anti-inflammatory agents of Rubin *et al.* with the non-antibiotic antimicrobial agents and particle size of Schmitt *et al.* and the other agents disclosed in Saunders Manual to treat sinusitis with the reasonable expectation of preparing formulations with multiple active agents which make the treatment more effective and potent. Further, the Examiner concludes that one of ordinary skill in the art would have been motivated to optimize the osmotic pressure, pH and NaCl equivalency of the composition, by routine experimentation to include a wider range for different drugs.

The Examiner's rejection is respectfully traversed because the Examiner has not met the burden of establishing some suggestion or motivation to combine the cited references, and even if the motivation to combine the cited references was established, which it is not, the references relied upon by the Examiner, either alone or in combination, fail to teach or suggest every element of the Applicants' presently claimed method.

(i) The Amended Claims are Directed to Methods of Treating Chronic Sinusitis Comprising the Nasal Administration of an Aerosolized Composition Comprising Betamethasone and a Surfactant having a Specific Surface Tension which Provides For Deposition, Penetration, or Retention of the Composition in the Nasal Sinuses

Independent claim 67 has been amended and is directed to a method of treating chronic sinusitis comprising the step of (1) nasally administering an aerosolized pharmaceutical composition to a mammal diagnosed or suspected of having chronic sinusitis, (2) wherein the composition comprises betamethasone; and a surfactant, (3) wherein the composition is formulated for nasal administration as an aerosolized composition and (4) has a surface tension of about 10 to about 70 dynes/cm, (5) wherein the surface tension is effective for deposition, penetration or retention of the composition in the nasal sinuses, whereby the aerosolized pharmaceutical composition is effective

for treatment of chronic sinusitis. The claims which depend from claim 1, claims 67-69, 73-85, 87, 90-110, 112, and 113, specify particulars regarding the methods of treating chronic sinusitis.

(ii) There Would Have Been No Motivation to Have Combined the Teachings of Rubin et al. With Those of Schmitt et al. and Saunders Manual to Arrive at the Presently Claimed Methods

Rubin *et al.* and Schmitt *et al.* focus on the treatment of lung conditions, such as chronic lung diseases and pulmonary infections, by enhancing the penetration of an active agent into both *the lower respiratory tract* and *peripheral areas of the lung*, either by lowering the surface tension of the formulation by the addition of a surfactant or by the use of a narrow particle size range, respectively. Neither reference, singly or in combination, teaches or suggests methods for delivery of agents to *the nasal sinuses* for the treatment of chronic sinusitis. Moreover, neither reference, singly or in combination, teaches or suggests methods for the use of an aqueous composition comprising betamethasone and a surfactant, wherein the composition has a surface tension of between about 10 to about 70 dynes/cm for the treatment of chronic sinusitis.

Saunders Manual teaches only treatments for acute sinusitis and does not address treatments of chronic sinusitis or the need of treatments for chronic sinusitis. Moreover, Saunders Manual does not address treatments of lung disease. Saunders Manual merely teaches general diagnosis and treatment of sinusitis.

Thus, there is no motivation or suggestion in any of the cited references to have combined the teachings of Rubin *et al.* and Schmitt *et al.* with those of the Saunders Manual to arrive at the instantly claimed methods since Rubin *et al.* and Schmitt *et al.* are concerned with enhancing deep lung penetration of an active ingredient for the treatment of chronic lung diseases and pulmonary infections and the Saunders Manual is directed to the treatment of acute sinusitis. For at least these reasons, the Examiner has failed to meet the burden of establishing "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings." *See In re Rouffet*, 149 F.3d

1350, 1357 (Fed. Cir. 1998). Accordingly, the rejection of claim 67, under 35 U.S.C. § 103(a) is improper and should be reversed.

(iii) Rubin et al. in view of Schmitt et al. and Saunders Manual of Medical Practice Do Not Teach or Suggest the Presently Claimed Methods

As amended, Applicants' pending claims are directed to methods of treating chronic sinusitis comprising the step of nasally administering an aerosolized pharmaceutical composition to a mammal diagnosed or suspected of having chronic sinusitis, wherein the composition comprises, *inter alia*, betamethasone and a surfactant, wherein the composition is formulated for nasal administration as an aerosolized composition and *has a surface tension of about 10 to about 70 dynes/cm*, wherein the surface tension is effective for *deposition, penetration or retention of the composition in the nasal sinuses*.

U.S. Pat. No. 5,925,334--"Rubin et al."

Rubin *et al.* do not disclose methods of treating chronic sinusitis by nasally administering an aerosolized pharmaceutical composition comprising betamethasone with a surfactant to modify the surface tension of the composition such that the composition as formulated has a surface tension of between about 10 to about 70 dynes/cm to provide for effective deposition, penetration or retention of the composition in the nasal sinuses. Thus, Rubin *et al.* do not teach or make obvious Applicants' claimed methods. To the contrary, Rubin *et al.* teach that surfactants can be used to lower the surface tension of a compositions comprising medications to enhance the distribution and spreading of the medications *to the lower respiratory tract*. As such, Rubin *et al.* actually teach away from the presently claimed methods by teaching the use of surfactants to modify surface tension of a formulation to provide distribution of medication to the lower respiratory tract, whereas Applicants' presently claimed methods utilize a surfactant formulation an aqueous composition to have a surface tension of between about 10 to about 70 dynes/cm to provide effective deposition, penetration or retention *in the nasal sinuses*, not the lower respiratory tract. Moreover, Rubin *et al.* merely states that surfactants can be used as surface tension lowering agents to enhance distribution of medication to the lower respiratory tract. Thus, not only is Rubin *et al.* silent on the use of surfactants to

formulate an aqueous composition for deposition, penetration, or retention of the composition in the nasal passages, but Rubin *et al.* is completely void of any ranges of surface tension that may enable the deposition, penetration, or retention of a composition in the nasal passages.

U.S. Pat. No. 4,950,477--“Schmitt *et al.*”

Schmitt *et al.* fail to cure the deficiencies of Rubin *et al.* As discussed above, Examiner relies on Schmitt *et al.* solely for the proposition that a particle size of between 0.5 μm and 8.0 μm is necessary for the particles to *reach the periphery of the lungs and be retained therein* to achieve a therapeutic effect in the prevention or treatment of an infection within the lung. Thus, Schmitt *et al.* likewise fail to teach or suggest a method of treating chronic sinusitis by nasally administering an aerosolized pharmaceutical composition comprising betamethasone with a surfactant to modify the surface tension of the composition such that the composition as formulated has a surface tension of between about 10 to about 70 dynes/cm to provide for effective deposition, penetration or retention of the composition in the nasal sinuses. In fact, a close analysis of Schmitt *et al.* reveals that this reference is completely void of any reference to surface tension as a parameter to provide for effective deposition, penetration or retention of a composition in the nasal sinuses. Moreover, Schmitt *et al.* merely teach the optimization of particle size to between 0.5 μm and 8.0 μm to allow for penetration of a polyene or derivative thereof (not a steroidal anti-inflammatory such as betamethasone) to the peripheral areas of the lung, *i.e.*, deep lung penetration. Thus, not only does Schmitt *et al.* fail to even mention surface tension as a parameter of a formulation, the alleged disclosure of Schmitt *et al.* is directed, not to deposition, penetration or retention of the composition in the nasal sinuses (as is presently claimed), but to the optimization of particle size to achieve deep lung penetration of a polyene or derivative thereof to treat lung infection. As such, Schmitt *et al.* fails to teach or suggest a method of treating chronic sinusitis by nasally administering an aerosolized pharmaceutical composition comprising betamethasone with a surfactant to modify the surface tension of the composition such that the composition as formulated has a surface tension of between about 10 to about 70 dynes/cm to provide for effective deposition, penetration or retention of the composition in the nasal sinuses, as required by the presently pending claims.

Saunders Manual of Medical Practice

Saunders Manual of Medical Practice fails to cure the deficiencies of both Rubin *et al.* and Schmitt *et al.*, or any combination thereof. As stated above, the Examiner relies on Saunders Manual merely to teach the state of the art regarding sinusitis. Saunders Manual is completely silent with regard to the use of surfactants to formulate an aqueous composition for deposition, penetration, or retention of the composition in the nasal passages. Moreover, Saunders Manual is completely silent with regard to effect of surface tension on the ability of a composition to be deposited, penetrated, or retained in the nasal passages. As such, the Saunders Manual fails to teach or suggest a method of treating chronic sinusitis by nasally administering an aerosolized pharmaceutical composition comprising betamethasone with a surfactant to modify the surface tension of the composition such that the composition as formulated has a surface tension of between about 10 to about 70 dynes/cm to provide for effective deposition, penetration or retention of the composition in the nasal sinuses, as required by the presently pending claims.

As explained *supra*, the art cited by the Examiner, when taken alone or in combination, fails to teach or suggest all of the claim elements of claim 67. An obviousness rejection, among other things, requires that *all* of the claim elements be taught or suggested by the cited references. *See In re Royka*, 490 F.2d, 984-85 (CCPA 1974). Since all elements of claim 67 are not taught or suggested by the references relied on in the rejection, claim 67, and claims 68-69, 73-85, 87, 90-110, 112, and 113 that depend from claim 67, are not obvious over the references cited by the Examiner.

Robert S. OSBAKKEN et al.
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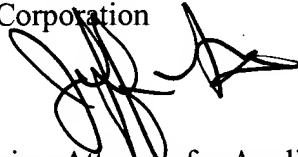
Attorney's Docket No.: 28450-703.201

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (858) 350-2307.

Respectfully submitted,

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A handwritten signature in black ink, appearing to read 'Jeffrey W. Guise', is written over the text of the firm name.

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